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Original Contribution

Serum Retinol and Risk of Prostate Cancer

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Greater exposure to retinol (vitamin A) may prevent prostate cancer, although under some conditions it could promote cell growth and de-differentiation. The authors prospectively examined prostate cancer risk and serum retinol levels, measured by using high-performance liquid chromatography, at baseline ($n = 29{,}104$) and after 3 years ($n = 22{,}843$) in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort. Cox proportional hazards models were used to estimate the relative risk of total ($n = 2{,}041$) and aggressive ($n = 461$) prostate cancer by quintiles of baseline and 3-year serum retinol concentrations and by change in serum retinol levels from baseline to 3 years. Men with higher retinol concentrations at baseline were more likely to develop prostate cancer (quintile 5 vs. quintile 1 hazard ratio = 1.19, 95% confidence interval: 1.03, 1.36; $P_{trend} = 0.009$). The results were similar for aggressive disease. Joint categorization based on baseline and 3-year retinol levels showed that men who were in the highest quintile at both time points had the greatest increased risk (baseline/3-year quintile 5/quintile 5 vs. quintile 1/quintile 1 hazard ratio = 1.31, 95% confidence interval: 1.08, 1.59). In this largest study to date of vitamin A status and subsequent risk of prostate cancer, higher serum retinol was associated with elevated risk, with sustained high exposure conferring the greatest risk. Future studies may clarify the underlying biologic mechanisms of the retinol-prostate cancer association.

cohort studies; prospective studies; prostatic neoplasms; vitamin A

Abbreviation: ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention.

Although antioxidant micronutrients are thought to reduce the risk of prostate cancer, the evidence for most such associations remains inconclusive. Retinol, the most biologically active form of vitamin A, has been hypothesized to prevent cancer at various sites, including the prostate, by promoting cell differentiation and apoptosis, increasing levels of other antioxidants, and regulating DNA transcription by inhibiting DNA polymerase activity (1). On the other hand, there is evidence that under some conditions, retinol may stimulate growth and de-differentiation of prostate cells (2).

Observational studies of dietary or supplemental intake of retinol or proretinol carotenoids and risk of prostate cancer have shown mixed results (3–25). Supplementation trials of β-carotene (a carotenoid that can be cleaved to form 2 retinol molecules) have found either no overall effect (26, 27) or a non-statistically significantly higher incidence of prostate cancer (28). Because the release of retinol into the circulation from the liver is tightly regulated, however, there is a low correlation between dietary or supplemental intake and circulating concentrations of retinol (29). Circulating concentrations of retinol are influenced by many factors in addition to diet and supplement use, including those related to absorption of these compounds from the gut, cleavage of proretinol compounds to form retinol, transport to and from stores in the liver, and inflammation and infections (30). Thus, circulating retinol concentration is a more direct measure of retinol status than self-reported dietary or supplemental intake.

Results from epidemiologic studies of circulating retinol concentration and prostate cancer have also been mixed, with most studies finding no association (31–39) and other studies finding an inverse association (40–45) or a positive association (46, 47). Many of these investigations were relatively small (7 of them included fewer than 100 prostate

cancer cases) (31, 33, 40, 41, 44–46) and thus may have been underpowered to detect modest associations or to conduct biologically relevant subgroup analyses. Further, none of these studies examined retinol measured at more than 1 point in time. Because investigation of the circulating retinol-prostate cancer association in a cohort with a large number of prostate cancer cases and more than 1 exposure measurement would address these issues, we analyzed data from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a large primary prevention trial of α-tocopherol and β-carotene supplementation in Finnish men.

MATERIALS AND METHODS

Study population

The ATBC Study was a randomized, double-blind, placebo-controlled, primary prevention trial conducted to determine the effects of supplementation with α-tocopherol and β-carotene on cancer incidence. In all, 29,133 white male smokers from southwestern Finland were recruited between 1985 and 1988. Enrollment criteria included age between 50 and 69 years and smoking of at least 5 cigarettes per day. Men were ineligible if they had previously had cancer, had another serious illness at enrollment, or reported current daily use of supplements containing vitamin E (>20 mg), vitamin A (>20,000 IU), or β-carotene (>6 mg). Men who were enrolled in the trial were assigned to 1 of 4 groups on the basis of a 2 × 2 factorial design: 1) α-tocopherol (dl-α-tocopherol acetate, 50 mg/day), 2) β-carotene (20 mg/day), 3) both supplements, or 4) placebo. Trial participants took the capsules for 5–8 years (median, 6.1 years), until death, or until the trial ended on April 30, 1993.

At enrollment, participants completed questionnaires about general risk factors, smoking, and medical history, as well as a validated food frequency questionnaire. Participants underwent a physical examination at baseline, during which registered nurses measured their height and weight and collected an overnight fasting blood sample. Fasting blood samples were collected again 3 years into the study. Although the trial has ended, follow-up is ongoing through the Finnish Cancer Registry and the Register of Causes of Death. As of April 30, 2006, a total of 2,041 incident prostate cancer cases occurred during 417,532 person-years of follow-up. Men were excluded from this analysis if they had missing or invalid (i.e., below the limit of detection) information on baseline serum retinol concentration ($n = 29$), leaving 2,041 cases among 29,104 men and 417,220 person-years for baseline analyses and 1,732 cases among 22,843 men and 349,353 person-years for analyses using the 3-year follow-up measurement.

The ATBC Study was approved by institutional review boards at both the US National Cancer Institute and the Finnish National Public Health Institute, and written informed consent was obtained from all participants.

Exposure and outcome assessment

Prostate cancer cases were identified through linkage with the Finnish Cancer Registry, which provides nearly 100% complete incident cancer ascertainment in Finland (48). Medical records for the cases diagnosed before September 2001 were reviewed by 1 or 2 study oncologists to confirm diagnosis and staging; when available, pathologic specimens were reviewed by a pathologist. For cases diagnosed after September 2001, only the information from the Finnish Cancer Registry is available. Cases were defined as ''aggressive'' if they were TNM Classification of Malignant Tumors stage III or IV, American Joint Committee on Cancer stage 3 or higher, or Gleason sum 8 or higher. Stage or Gleason sum information was available for 63% of the cases.

As part of the intervention protocol to assess the influence of the supplemental β-carotene, serum retinol concentration was measured for all trial participants at enrollment and again after 3 years of follow-up. Assays were conducted over a several-year period in one dedicated laboratory at the National Public Health Institute in Helsinki, Finland, that was certified through a National Institute of Standards and Technology quality-control testing program. Retinol was measured in fasting serum samples by using isocratic high-performance liquid chromatography (49). All samples were protected from light and stored at −70°C until they were assayed within 2–4 years of serum collection. The study samples from the cohort members were sequentially batched in the order in which they were collected and transported to the institute's central laboratory from the study centers. Quality-control samples were embedded in each batch, and the laboratory was blinded to the samples' quality-control status. The quality-control samples included internal standards, individual quality-control duplicate aliquots, and external reference samples provided by the National Institute of Standards and Technology as part of the quality-control program for β-carotene, retinol, and other micronutrients. The between-run coefficient of variation was 2.4%, and the overall coefficient of variation was 2.2%. The intraclass coefficient for correlation between the baseline and 3-year retinol measurements was 80.1%. The limit of detection was 20 μg/L.

Statistical analysis

Cox proportional hazards modeling was used to estimate the association between quintiles of baseline serum retinol concentration (quintile 1, <483 μg/L; quintile 2, 483–546 μg/L; quintile 3, 547–606 μg/L; quintile 4, 607–684 μg/L; and quintile 5, ≥685 μg/L) and risk of total prostate cancer ($n = 2,041$) and aggressive disease ($n = 461$). Men for whom information on disease aggressiveness was not available were excluded from analyses of aggressive disease. All models were adjusted for age at baseline as a continuous variable. The following factors, which are hypothesized or known to be associated with either prostate cancer or retinol, were assessed as potentially confounding variables: α-tocopherol treatment group, β-carotene treatment group, total cholesterol level, serum α-tocopherol, serum β-carotene, number of cigarettes smoked per day, years spent smoking, family history of prostate cancer, physical activity, body mass index, height, weight, educational level, marital status, urban residence, total energy intake, total fat intake, fruit intake, vegetable intake, red meat intake, dietary retinol intake, dietary vitamin D intake, dietary calcium intake, supplemental vitamin A intake, supplemental vitamin

Table 1. Age-Adjusted[a] Baseline[b] Characteristics of Study Participants by Quintile of Baseline Serum Retinol, in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, 1985–2006

Characteristic	Quintile of Serum Retinol Level, μg/L														
	Quintile 1 (<483)			Quintile 2 (483–546)			Quintile 3 (547–606)			Quintile 4 (607–684)			Quintile 5 (≥685)		
	No.	%	Mean	No.	%	Mean	No.	%	Mean	No.	%	Mean	No.	%	Mean
Age, years			58			57			57			57			56
Height, cm			173			174			174			174			174
Weight, kg			77.0			78.7			79.6			80.0			81.1
Body mass index[c]			25.6			26.1			26.3			26.5			26.8
Serum cholesterol, mmol/L			5.8			6.1			6.3			6.4			6.5
Serum α-tocopherol, mg/L			10.8			11.5			12.0			12.3			13.0
Serum β-carotene, μg/L			210			218			221			215			196
No. of cigarettes smoked per day			20.4			20.3			20.3			20.5			20.6
Years of smoking			36.5			36.3			35.9			35.6			35.4
Family history of prostate cancer	107	3.1		111	3.0		109	2.8		141	3.7		150	4.1	
Physically active	1,026	19.3		1,225	21.8		1,242	21.2		1,312	21.6		1,240	19.7	
Greater than an elementary school education	1,056	18.5		1,048	18.3		1,196	20.5		1,322	22.4		1,497	25.2	
Married	4,545	77.9		4,671	80.9		4,755	81.4		4,735	81.0		4,638	79.5	
Urban residence	3,539	61.2		3,345	58.0		3,460	59.3		3,365	57.5		3,488	59.6	
Daily dietary, and supplement intake															
Total energy, kcal			2,681			2,702			2,698			2,702			2,659
Total fat, g			101.6			102.5			101.9			101.1			97.9
Dietary retinol, μg			1,436			1,476			1,497			1,528			1,559
Supplemental vitamin A, μg			114			118			137			153			183
Dietary vitamin D, IU			5.3			5.3			5.3			5.5			5.5
Supplemental vitamin D, μg			0.66			0.71			0.83			0.88			1.20
Dietary calcium, mg			1,371			1,398			1,391			1,412			1,381
Supplemental calcium, mg			9.1			9.3			2.8			3.3			4.0
Fruit, g			216			218			220			217			218
Vegetables, g			286			292			296			297			294
Red meat, g			70.3			71.3			71.7			71.5			71.4
Alcohol consumption, g			13.9			14.6			16.7			19.6			24.8

[a] Directly standardized to the age distribution of the entire cohort.

[b] Data on all characteristics were from the baseline questionnaire except family history, for which data were collected during follow-up and were available for 18,722 men. Baseline dietary data were available for 27,111 men, and 5,516 men claimed some supplement use at baseline.

[c] Weight in kilograms divided by height in meters squared.

Table 2. Age-Adjusted Hazard Ratios for Serum Retinol (μg/L) and Risk of Overall and Aggressive Prostate Cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, 1985–2006

	All Prostate Cancer				Aggressive Prostate Cancer[a]			
	No. of Cases	Person-Years	HR	95% CI	No. of Cases	Person-Years	HR	95% CI
Baseline								
Quintile 1: <483	362	78,231	1.0	Referent	86	67,179	1.0	Referent
Quintile 2: 483–546	397	82,429	1.05	0.91, 1.21	74	69,543	0.85	0.63, 1.17
Quintile 3: 547–606	413	85,271	1.06	0.92, 1.22	104	71,449	1.19	0.89, 1.58
Quintile 4: 607–684	434	86,050	1.13	0.98, 1.30	97	72,071	1.13	0.85, 1.51
Quintile 5: ≥685	435	85,239	1.19	1.03, 1.36	100	71,300	1.22	0.92, 1.63
P trend				0.009				0.05
Follow-up (3 years)[b]								
Quintile Q1: <494	312	66,010	1.0	Referent	66	56,203	1.0	Referent
Quintile 2: 494–559	332	70,612	0.99	0.85, 1.16	70	59,220	1.03	0.73, 1.44
Quintile 3: 560–622	383	70,736	1.17	1.01, 1.36	90	58,929	1.38	1.00, 1.89
Quintile 4: 623–704	328	71,248	1.01	0.86, 1.18	66	59,270	1.01	0.72, 1.43
Quintile 5: ≥705	377	70,747	1.22	1.05, 1.41	85	59,071	1.38	1.00, 1.91
P trend				0.02				0.09
3-year change (follow-up to baseline)								
<−75	262	53,849	1.08	0.88, 1.31	64	45,495	1.05	0.70, 1.58
−75 to −11	429	82,672	1.09	0.91, 1.32	86	68,963	0.90	0.61, 1.32
−10 to 9	150	32,149	1.0	Referent	37	26,889	1.0	Referent
10 to 74	488	98,162	1.04	0.87, 1.25	109	81,773	0.96	0.66, 1.39
≥75	403	82,520	1.07	0.89, 1.29	81	69,574	0.86	0.59, 1.27
P trend				0.78				0.35

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Information on cancer stage and grade was available for cases diagnosed through July 2002.

[b] Based on 22,843 men in active follow-up through the third year-blood collection.

D intake, and supplemental calcium intake. Each variable was entered into the age-adjusted model to evaluate whether the point estimates for retinol categories changed by at least 10%, and none did so. Thus, our final model was adjusted for age only. We also present our primary findings adjusted for all potentially confounding factors to show that addition of those factors did not appreciably alter the results. We confirmed the proportional hazards assumption by including in the model term for interaction between serum retinol and follow-up time and testing that term by using the Wald test (*P*-interaction = 0.45).

To examine the associations between prostate cancer risk and low and high extremes of serum retinol levels, we also evaluated retinol deciles. The inferences were similar using these cutpoints, so we present our results for baseline serum retinol in quintiles. We also examined the association between risk and quintiles of serum retinol on the basis of concentrations measured in blood from the 3-year follow-up visit (i.e., <494, 494–559, 560–622, 623–704, and ≥705 μg/L), as well as with quintiles of the average of the retinol concentration measured at baseline and at the follow-up visit (i.e., <498, 498–558, 559–614, 615–688, and ≥689 μg/L). We obtained identical results when we categorized the 3-year serum retinol measurement using the baseline cutpoints; thus, we retained the distinct 3-year cutpoints described above for analysis. We further examined prostate cancer risk in relation to the difference in serum retinol between the baseline and 3-year measurement, both as categories of the 3-year concentration minus baseline concentration (i.e., <−75, −75 to −11, −10 to 9, 10 to 74, and ≥75 μg/L) and through joint classification based on the baseline and 3-year measurements.

Exploratory subgroup analyses were conducted by stratifying by follow-up time (<10 years vs. ≥10 years), age at prostate cancer diagnosis (<60 years vs. ≥60 years), cigarettes smoked per day (<10, 10–19, 20−39, or ≥40), years spent smoking (<36 vs. ≥36), pack-years of smoking (<35 vs. ≥35), family history of prostate cancer, intervention arms (α-tocopherol vs. β-carotene), less than median vs. greater than or equal to median of body mass index, serum α-tocopherol, serum β-carotene, serum total cholesterol, use of supplemental vitamin A or vitamin D, and dietary intake of retinol, vitamin E, vitamin A, vitamin D, and alcohol. Statistical interaction was assessed using the likelihood ratio test. We considered $\alpha = 0.05$ to be the threshold for statistical significance in all analyses.

RESULTS

Men with higher baseline serum retinol levels had greater average body mass indexes, serum cholesterol levels, serum

Table 3. Age-Adjusted Hazard Ratios for Prostate Cancer, by Joint Categories of Baseline and Follow-Up Serum Retinol, in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, 1985–2006

Quintile of Baseline Serum Retinol Level	Quintile of Follow-up (3-Year) Serum Retinol Level				
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Quintile 1					
No. of cases	180	69		52	
HR	1.0	0.92		1.09[a]	
95% CI	Referent	0.70, 1.22		0.80, 1.48	
Quintile 2					
Cases	67	125	94	43	
HR	0.88	1.06	1.22	0.92[b]	
95% CI	0.66, 1.16	0.85, 1.34	0.95, 1.56	0.66, 1.29	
Quintile 3					
Cases	45	83	108	94	33
HR	1.36	0.99	1.03	1.16	1.05
95% CI	0.98, 1.88	0.76, 1.28	0.81, 1.30	0.91, 1.49	0.72, 1.52
Quintile 4					
Cases	61		102	106	90
HR	1.09[c]		1.26	0.94	1.14
95% CI	0.81, 1.45		0.99, 1.61	0.74, 1.19	0.88, 1.47
Quintile 5					
Cases		54		90	236
HR		1.10[d]		1.11	1.31
95% CI		0.81, 1.49		0.86, 1.43	1.08, 1.59

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Estimate for baseline/3-year quintile 1/quintiles 3–5.
[b] Estimate for baseline/3-year quintile 2/quintiles 4–5.
[c] Estimate for baseline/3-year quintile 4/quintiles 1–2.
[d] Estimate for baseline/3-year quintile 5/quintiles 1–3.

α-tocopherol levels, and dietary intakes of retinol and alcohol, were more likely to have a family history of prostate cancer and to be more educated, and used less supplemental calcium and more supplemental vitamin D and vitamin A than men with lower serum retinol (Table 1). However, there were no meaningful correlations between serum retinol concentration and intake of dietary vitamin A ($r = 0.05$, $P < 0.0001$) or supplemental vitamin A ($r = 0.05$, $P < 0.0001$) and serum β-carotene ($r = -0.04$, $P < 0.0001$). By contrast, serum retinol was weakly correlated with serum α-tocopherol level ($r = 0.23$, $P < 0.0001$) and serum total cholesterol level ($r = 0.22$, $P < 0.0001$). Baseline and 3-year follow-up serum retinol concentrations were well-correlated ($r = 0.68$, $P < 0.0001$).

Men in the highest quintile of baseline serum retinol were significantly more likely to develop prostate cancer during the follow-up period than were men in the lowest quintile, and a dose-risk relation was evident (Table 2). The association was unchanged when we adjusted for all potentially confounding factors (quintile 5 vs. quintile 1 hazard ratio = 1.18, 95% confidence interval: 1.01, 1.38; P trend = 0.02). The association also did not change when we excluded either men who did not have blood collected during follow-up at 3 years ($n = 6{,}261$) or men whose serum retinol measurements were in the top or bottom 1% of the distribution ($n = 588$) (data not shown). The positive association was similar for aggressive prostate cancer and when either the 3-year serum retinol measurement (Table 2) or the average of the baseline and 3-year measurements (quintile 5 vs. quintile 1 hazard ratio = 1.24, 95% confidence interval: 1.07, 1.44; P trend = 0.01) was used instead of the baseline concentration. Absolute change in serum retinol concentration from baseline to 3 years was not associated with prostate cancer risk (Table 2).

Joint categorization of men based on quintiles of the baseline and follow-up serum retinol concentrations revealed that men in the highest quintile at both time points had the greatest increase in risk of prostate cancer (for individuals who were in the fifth quintile at both time points vs. those who were in the first quintile at both time points, hazard ratio = 1.31, 95% confidence interval: 1.08, 1.59) (Table 3). Men in some other baseline-3-year retinol categories were also at a somewhat increased risk, but with no distinct pattern (Table 3).

We tested for effect modification by relevant factors, and although none of the interactions were statistically significant, our results suggested that the positive serum retinol-prostate cancer association was strongest among men who were in the placebo and α-tocopherol-only groups (i.e.,

Table 4. Age-Adjusted Hazard Ratios of Collapsed Quintiles of Baseline Serum Retinol (μg/L) and Total Prostate Cancer, Stratified by Potential Effect Modifiers[a], in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, 1985–2006

Subgroup	Cases	Category of Baseline Serum Retinol Level, μg/L						*P* for Interaction
		Quintile 1[b] (<483)		Quintiles 2 and 3 (483–606)		Quintiles 4 and 5 (≥607)		
		HR	95% CI	HR	95% CI	HR	95% CI	
Trial supplementation group								
Placebo	532	1.0	Referent	1.08	0.84, 1.38	1.28	1.01, 1.64	
β-carotene only	531	1.0	Referent	1.08	0.85, 1.38	1.14	0.90, 1.45	
α-tocopherol only	480	1.0	Referent	1.09	0.84, 1.41	1.22	0.95, 1.58	
α-tocopherol and β-carotene	498	1.0	Referent	0.98	0.77, 1.24	1.00	0.78, 1.27	0.82
Serum α-tocopherol, mg/L								
<11.5	1,026	1.0	Referent	1.06	0.91, 1.24	1.09	0.92, 1.29	
≥11.5	1,015	1.0	Referent	1.08	0.88, 1.33	1.28	1.06, 1.56	0.26
Serum β-carotene, μg/dL								
<170	921	1.0	Referent	0.95	0.79, 1.14	1.03	0.86, 1.23	
≥170	1,120	1.0	Referent	1.15	0.97, 1.36	1.28	1.08, 1.52	0.21
Serum total cholesterol, mmol/L								
<6.15	988	1.0	Referent	0.98	0.83, 1.15	1.09	0.92, 1.29	
≥6.15	1,053	1.0	Referent	1.16	0.95, 1.41	1.25	1.03, 1.52	0.42
Dietary retinol intake, μg/day								
<1,246	1,031	1.0	Referent	0.96	0.81, 1.15	1.09	0.91, 1.30	
≥1,246	1,010	1.0	Referent	1.14	0.95, 1.37	1.20	1.00, 1.44	0.41
Supplemental vitamin A								
No	1,795	1.0	Referent	1.10	0.96, 1.25	1.18	1.03, 1.35	
Yes	229	1.0	Referent	0.69	0.47, 0.99	0.88	0.62, 1.24	0.07
Dietary vitamin D, IU/day								
<4.7	1,092	1.0	Referent	1.02	0.85, 1.21	1.12	0.94, 1.33	
≥4.7	949	1.0	Referent	1.09	0.90, 1.31	1.17	0.97, 1.40	0.89
Supplemental vitamin D								
No	1,875	1.0	Referent	1.06	0.93, 1.21	1.17	1.03, 1.33	
Yes	149	1.0	Referent	0.83	0.53, 1.32	0.83	0.53, 1.30	0.38
Alcohol intake, g/day								
<11	1,119	1.0	Referent	1.10	0.93, 1.29	1.19	1.00, 1.41	
≥11	922	1.0	Referent	0.97	0.79, 1.20	1.08	0.88, 1.31	0.61

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Subgroups were based on median values unless otherwise noted.
[b] The first quintiles served as the referent category.

those not receiving the β-carotene supplement), men with high baseline serum α-tocopherol, β-carotene, or total cholesterol levels, and men who had high dietary retinol intake (Table 4). We observed a borderline statistically significant interaction with vitamin A use, with a positive association between serum retinol and prostate cancer among men who did not take vitamin A supplements at study entry (Table 4). A similar association was observed when we stratified by vitamin D supplement use; however, 98.7% of men taking supplemental vitamin D were also taking vitamin A, most in the form of a multivitamin (data not shown). There was no interaction between serum retinol concentration, prostate cancer, and the other factors examined, and the subgroup findings described were similar with respect to aggressive prostate cancer (data not shown).

DISCUSSION

To the best of our knowledge, this is the largest study of the association between circulating retinol concentration and incident prostate cancer to date. We observed a positive relation between retinol concentrations and subsequent risk of both total and aggressive prostate cancer, with a 20% greater overall risk for men in the highest retinol quintile. The present study may also be the first to have examined prostate cancer risk in relation to retinol concentration

measured from 2 blood samples collected years apart. Although we observed no association between prostate cancer risk and absolute change in retinol over time, our data indicate that men with sustained exposure to high serum retinol may be at the greatest increased risk of prostate cancer.

The biologic mechanism through which higher circulating retinol might increase the risk of prostate cancer is unknown and will require further basic or clinical study. Although retinol and other retinoids are generally hypothesized to be anticarcinogenic (1), some laboratory experiments have shown increased cell proliferation and de-differentiation in response to retinol that could contribute to tumorigenesis (2). These hypotheses, however, assume that higher circulating retinol concentrations correlate with higher intraprostatic retinol concentrations. Freeman et al. (50) examined the correlation between serum retinol and prostatic retinol concentrations and found it to be relatively low and inverse in nature ($r = -0.16$, $P > 0.05$), which could be consistent with a true retinol benefit at the prostate tissue level and a paradoxical positive serum association. Alternatively, it is possible that retinol influences prostate cancer risk through sex steroid, membrane, or other cell-signaling changes.

Although our findings are consistent with 2 reports of a positive association between serum retinol concentration and prostate cancer risk (46, 47), most studies showed no association (31–39) or an inverse association (40–45). There are a few reasons why we might have observed an association that differed from the latter studies. First, our cohort investigation, with over 2,000 incident prostate cancer cases is the largest conducted to date, and the 20% excess risk we noted for men with the highest vitamin A status was modest. Thus, most of the prior studies of smaller sample sizes likely were underpowered to ascertain a true association of the magnitude observed here. Another reason could relate to the fact that our study population was composed entirely of smokers, whereas most other studies had a relatively low prevalence of smoking. Metabolism of carotenoids to procarcinogenic compounds by cigarette smoke and aberrant cell proliferation have been suggested as mechanisms by which high-dose β-carotene supplements may increase lung carcinogenesis (51, 52), and it is possible that a similar smoking-retinol (or β-carotene) interaction occurs in other organs, including the prostate. Alternatively, male smokers have been shown to have higher levels of circulating sex steroid hormones, including testosterone (53), and perhaps retinol acts synergistically through this mechanism. Importantly, our finding that men with high serum retinol levels both at baseline and after 3 years had the greatest increased risk of prostate cancer is consistent with a true biologic influence of retinol in the etiology of prostate cancer.

Although we observed no statistically significant interactions, there was a suggestion that the increased risk observed with higher serum retinol levels was restricted to certain biologically relevant subgroups, such as men who were not randomized to receive the β-carotene trial supplement. As previously reported, men randomized to the β-carotene supplement in the ATBC Study had higher prostate cancer incidence (albeit not statistically significantly higher) than did men not receiving β-carotene supplements (28). Here, high serum retinol concentrations did not confer additional prostate cancer risk in the trial's β-carotene arm, suggesting that vitamin A status and β-carotene supplements acted through the same (or a similar) pathway to increase risk. The stronger retinol association in the high serum α-tocopherol and cholesterol strata could be consistent with some interference with the serum vitamin E prostate cancer benefit previously observed in this cohort (28, 54). Because these interactions were not statistically significant, however, our results could instead be explained by chance.

Our study had many strengths, including a large cohort and incident case sample size, complete population-based case ascertainment, information and measurements for many potential confounders and effect modifiers, and measurement of serum retinol for the entire available cohort at 2 points in time (albeit 3 years apart early in follow-up) uniformly in one dedicated laboratory. Ideally, we would like to be able to examine the risk associations of retinol at multiple time points during an extended period. The fact that our findings based on the 3-year serum determination replicated those from the baseline measurements to some degree validates the use of serum biomarkers from the time of enrollment into the ATBC Study. Further, prostate-specific antigen screening is not routinely done in Finland, making any detection bias of these retinol findings unlikely. One potential limitation of our study is that our population consisted entirely of smokers, which could limit the generalizability of our findings. However, the fact that we observed no interaction with the number of cigarettes smoked per day, duration of smoking, or pack-years of smoking argues against strong effect modification and nongeneralizability. Further, the distribution of serum retinol concentrations in our study was similar to that reported in other published studies from both the United States and Europe (34, 36, 37, 39, 44); small differences between populations could be due to laboratory differences.

In this population of male smokers, higher serum retinol concentrations were associated with a greater risk of prostate cancer over a 20-year period, with sustained high exposure conferring the greatest risk. We hypothesize that retinol could either directly impact prostate tumor growth and diagnosis or affect prostate tissue indirectly through a mechanism that influences both serum retinol and prostate cancer risk. Understanding the underlying biologic actions and their interactions with smoking and β-carotene supplementation may provide insight into prostate cancer etiology and prevention.

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